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In re Application of:

**André DELACOURTE**
**Nicolas SERGEANT**

Serial No.: **10/625,854**

Filed: **July 23, 2003**

For: **PREVENTION, TREATMENT AND DIAGNOSIS OF DISEASES ASSOCIATED WITH BETA-AMYLOID FORMATION AND/OR AGGREGATION**

§ Group Art Unit: **1649**

§ Examiner: **Chang Yu Wang**

§ Atty. Dkt. No.: **11362.0039.NPUS01**

§ Confirmation No.: **9442**

## SUPPLEMENTAL RULE 132 DECLARATION OF DR. EUGEEN VANMECHELEN

1. My name is Dr. Eugeen Vanmechelen. I am supplying this declaration in supplement to my earlier declaration dated 22 February 2007.

2. One key aspect of the Application is the detection and identification of N-terminal truncated forms of $A\beta_{42}$ in early stages of Alzheimer's pathology.

3. I understand that the Examiner has rejected certain claims in the Application directed to N-terminal truncated β-Amyloid variants for lack of enablement, in part, "[s]ince certain forms of Aβ42, such as Aβ8-42, Aβ11-42, Aβ10-42 variants, can also be detected in controls, they do not distinguish between the controls and AD" (Office Action mailed May 15, 2007, p. 4).

4. I have been instructed that for a U.S. patent claim to be enabled, the Application must enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the claimed invention.

5. In Figures 4 and 7 and Table 6, subjects designated as "controls" refer to a mixture of subjects that either underwent a normal aging process in the absence of tau pathology (S0), or those that have tau pathology (S1-S7) but are either clinically non-demented or in their preclinical stages of AD (*See* Delacourte et al. (1999)).

6. Figure 7 of the Application shows detection of N-terminally truncated $A\beta_{42}$ peptides in a variety of subjects, including some that are designated as "controls" in Table 6. (Table 6 describes results from experiments performed on tissue of the same deceased subjects). Detection of N-terminally truncated $A\beta_{42}$ peptides in patients designated as "controls" (*i.e.*, patients with tau pathology but no clinical impairment or dementia) is significant because the detection of $A\beta_{42}$ peptides in preclinical stages of AD (as assessed by tau pathology) provides an independent, early evaluation of progressing Alzheimer's pathology.

7. As described in the Application, Table 8 shows detection of Aβ 5-42, Aβ 8-42, Aβ 10-42 and Aβ 11-42 in cerebrospinal fluid (CSF) from in a variety of living patients that comprise a different patient cohort.

8. Detection of the indicated N-terminal truncated Aβ 8-42 peptides in one of the "control" patients of Table 8 (e.g., "control" Nr 148) is significant because this patient might be in either the preclinical or infraclinical stages of Alzheimer's disease; that is, where a combination of tau pathology and clinical assessment may not signal the subject's risk or susceptibility of Alzheimer's Disease. *See e.g.,* Braak E, et al., Neuropathology of

Alzheimer's disease: what is new since A. Alzheimer? *Clin. Neuroscience* (1999) 249: 14-22.

9. As shown in Figures 4 and 7 and Table 8, detection of Aβ peptide 8-42 in patients designated "S0" and "Control" is not a natural phenomenon because, as described above, there exist two populations of patients, both of which are clinically defined "control" based on tau pathology—one population that is defined as normal aging with no tau pathology, and one that has preclinical or infraclinical AD (as determined by tau pathology after death).

10. In the data presented in Figure 7, Table 6 and Table 8 there appears to be anomaly in that Aβ 8-42 is present in one of the control CSF samples (Control no. 148, Cru). I am of the opinion that this sample labelled as "control" is in fact a false negative control. In other words, this false negative "control" is a patient who did not exhibit any clinical symptoms of AD, but indeed was suffering from pathological changes.

11. Detection of Alzheimer pathology in elderly patients can only be done by examining the brain. However based on prospectively collected brains, researchers have suggested a highly selective disease process in the brain. This disease process was first described by Braak (Braak et al, 1999) and later confirmed by Delacourte (Delacourte et al., 1999; Delacourte et al., 2002; Deramecourt et al., 2006). Braak and colleagues have examined 3508 brains from age 25 till age 95 for the presence (or absence) of neurofibrillary changes. As expected the late stages (Braak stage III to VI) were only present in patients with Alzheimer's disease, while the 'preclinical' stages I and II were present at a much early age. Thus people in the ages 30 to 40 have 20-35% changes of having Alzheimer pathological changes in their brain without any clinical samples.

12. This same phenomenon was also observed in the prospective brain collection from Delacourte as presented in Table 8 of the Specification. Since in the CSF study, the control group was age-matched we could expect even a higher percentage of false-positive in this study (at least a one in three chance). Thus we consider the control positive for Aβ 8-42 in Figure 7, Table 6 and Table 8 as a false negative control, that is an elderly person with Alzheimer pathology in the brain, but without any clinical symptoms.

13. In my opinion, a person of ordinary skill in the art would recognize that detection of the described N-terminal truncated Aβ 8-42 species is useful for assessing risk or susceptibility to Alzheimer's disease in a living patient.

Reference List


1. Delacourte A, David JP, Sergeant N, Buee L, Wattez A, Vermersch P, Ghozali F, Fallet-Bianco C, Pasquier F, Lebert F, Petit H, Di Menza C (1999) The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 52: 1158-1165.

2. Delacourte A, Sergeant N, Champain D, Wattez A, Maurage CA, Lebert F, Pasquier F, David JP (2002) Nonoverlapping but synergetic tau and APP pathologies in sporadic Alzheimer's disease. Neurology 59: 398-407.

3. Deramecourt V, Bombois S, Maurage CA, Ghestem A, Drobecq H, Vanmechelen E, Lebert F, Pasquier F, Delacourte A (2006) Biochemical staging of synucleinopathy and amyloid deposition in dementia with lewy bodies. J Neuropathol Exp Neurol 65: 278-288.

4. Braak E, Griffing K, Arai K, Bohl J, Bratzke H, Braak H (1999) Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? Clin Neurosci 249: 14-22.

I DECLARE THAT ALL STATEMENTS MADE HEREIN OF MY OWN KNOWLEDGE ARE TRUE AND CORRECT, AND THAT ALL STATEMENTS MADE ON INFORMATION AND BELIEF ARE BELIEVED TO BE TRUE, AND FURTHER THAT I HAVE MADE THESE STATEMENTS WITH THE KNOWLEDGE THAT WILLFUL FALSE STATEMENTS AND THE LIKE SO MADE ARE PUNISHABLE BY FINE OR IMPRISONMENT, OR BOTH, UNDER SECTION 1001 OF TITLE 18 OF THE UNITED STATES CODE, AND THAT SUCH WILLFUL FALSE STATEMENTS MAY JEOPARDIZE THE VALIDITY AND/OR ENFORCEABILITY OF THIS APPLICATION OR ANY PATENT THAT MAY ISSUE THEREON.

As a person signing below:

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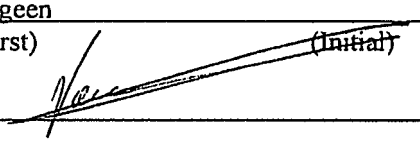
Signature: 

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